unique mass-to-charge ratio of the one or more analyte species.—

--46. (NEW) The method of claim 37 wherein the step of detecting the isolated one or more analyte species includes mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more analyte species by exhibiting a mass spectrometric response located at a unique mass-to-charge ratio of the one or more analyte species.—

--47. (NEW) The method of claim 41 wherein the step of detecting the isolated one or more analyte species includes mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more analyte species by exhibiting a mass spectrometric response located at a unique mass-to-charge ratio of the analyte species.—

REMARKS

In the Examiner's July 16, 2002 Office Action, the Examiner objected to Applicants' specification and rejected claims 31-44, which were renumbered as such by the Examiner. This Response amends claims 31-44 and presents new claims 45-47 for consideration. After entry of the foregoing amendment, claims 31-47 remain pending in the Application. Reconsideration is respectfully requested.

The specification was objected to due to various informalities pointed out by the Examiner. Applicant has amended the specification in accordance with the Examiner's suggestions as set out in the above amendments in order to overcome the Examiner's objection.

35 U.S.C. §112 Rejections

The Examiner rejected claims 33, 35, 38, 40 and 44 under 35 U.S.C. Section 112 , first paragraph, as containing subject matter not described in the specification in a way that could reasonably convey to one skilled in the art that Applicant had possession of the claimed subject matter. In response to the Examiner's rejection, Applicants have amended claims 33, 35, 38, 40,

42 and 44 to better define the subject matter contained in Applicants' specification.

The Examiner also rejected claims 31-44 under 35 U.S.C. section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specific instances are set out by the examiner at pages 4-6 of the Examiner's Office Action. In response to the Examiner's rejection, Applicants' have amended claims 31-44 to more specifically claim the subject matter of Applicants' invention.

35 U.S.C. §102(a) Rejections

Claims 31, 32, 36, 37 and 41 stand rejected under 35 U.S.C. §102(a) as being anticipated by *Nelson et al.* (Mass Spectrometric Immunoassay, Analytical Chemistry 1995, 67, 1153-1158), (hereinafter "*Nelson*"). Applicants respectfully traverse this rejection.

Under 35 U.S.C. Sec. 102(a), a person is entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. The *Nelson* journal article cited by the Examiner does not constitute a description of the invention in a printed publication before the invention was made by Applicants in that Applicants are the authors of the journal article, and Applicants conceived their invention before the publication of their journal article. Accordingly. Claims 31, 32, 36, 37 and 41 are not anticipated by *Nelson* and Applicants respectfully request the withdrawal of the Examiner's rejection under 35 U.S.C. Sec. 102(a).

35 U.S.C. §102(e) Rejections

Claims 31 and 36 stand rejected under 35 U.S.C. Sec. 102(e) as being anticipated by *Koster et al.*, U.S. Patent No. 5,605,798, issued Feb. 25, 1997 (hereinafter "*Koster*"). More specifically, the examiner states that *Koster* discloses a mass spectrometric method for determining if a particular analyte (nucleic acid sequence) is in a biological sample by using an affinity reagent (capture nucleic acid molecule) which has been immobilized to a solid support. The Examiner further asserts that *Koster* discloses that the method allows for the analyte to be detected and identified by its specific molecular weights. Applicants respectfully traverse this rejection.

35 U.S.C. Sec. 102(e) states that, "A person shall be entitled to a patent unless the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2) and (4) of section 371(c) of this title before the invention thereof by the applicant for patent." The standard for lack of novelty, that is, for "anticipation", is one of strict identity. "It is axiomatic that for prior art to anticipate under Section 102 it has to meet every element of the claimed invention, and that such a determination is one of fact." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

Koster discloses mass spectrometric processes for detecting a particular nucleic acid sequence in a biological. In one embodiment, a nucleic acid molecule containing the nucleic acid sequence to be detected (i.e. the target) is initially immobilized to a solid support. In other embodiments, such immobilization of the target nucleic acid molecule is optional.

Applicants' amended claims 31 and 36 include the step of capturing and isolating an analyte species from a specimen using an affinity reagent which includes at least one antibody immobilized onto a solid substrate. Using an affinity reagent which includes an antibody immobilized onto a solid substrate is directly opposite to the method disclosed in *Kostas* where the target nucleic acid molecule (or analyte) is immobilized to a solid support. Accordingly, *Kostas* fails to disclose each and every element of applicants' amended claims 31 and 36 and therefore cannot anticipate those claims. Therefore, Applicants respectfully request the withdrawal of the Examiner's 35 U.S.C. Sec. 102(e) rejection.

35 U.S.C. §103(a) Rejections

Claims 34, 39 and 43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Nelson* in view of *Papac et al.* (Direct analysis of Affinity-Bound analytes by MALDI/TOF MS, Analytical Chemistry 194, 66, 2609-2613) (hereinafter "*Papac*"). Claims 33, 38 and 42 also stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Nelson* in view of *Raybuck et al.*, U.S. Patent No. 5,833,927, issued November 10, 1998 (hereinafter "*Raybuck*"). Finally, claims 35, 40 and 44 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Nelson* in view of *Papac* as applied to claims 31, 32, 34, 36, 37, 39, 41 and 43 above, and further in view

of *Raybuck*. Applicants respectfully traverse all of the Examiner's 35 U.S.C. §103(a) rejections.

As previously pointed out above with reference to the Examiner's 35 U.S.C. Sec. 102(a) rejection, the *Nelson* reference does not constitute prior art for purposes of the Examiner's 35 U.S.C. Sec. 103(a) rejections because the *Nelson* publication was authored by the inventors and the inventors conceived of the invention prior to the publication. Accordingly, if the *Nelson* reference is removed from the Examiner's 35 U.S.C. Sec. 103(a) rejections, it would clearly not have been obvious to one of ordinary skill in the art to arrive at Applicants' claimed invention. Therefore, Applicants respectfully request the withdrawal of the Examiner's 35 U.S.C. Sec. 103(a) rejections.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current Amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Respectfully submitted,

By: Laura J. Zeman

Laura J. Zeman
Reg. No. 36,078

SNELL & WILMER L.L.P.
One Arizona Center
400 East Van Buren
Phoenix, Arizona 85004-2202
Telephone: (602) 382-6377
Facsimile: (602) 382-6070

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph starting on page 4, line 16, has been replaced with the following paragraph:

--While the new MALDI techniques opened the field of biomolecular mass spectrometry, the mass spectrometric analysis of complex biological materials was not possible because of matrix overloading. Recently, Hutchens et al. (Hutchens, T.W. and Yip, T., Rapid Communications in Mass Spectrometry, vol 7, 1993, pp. 576-580.) demonstrated the utilization of affinity capture methods to quasi-purify proteins in a specimen prior to MALDI mass spectrometry. By quasi-purifying the specimen being assayed Hutchens et al. effectively overcame the primary limitation of MALDI mass spectrometry, namely, the suppression of ion signal due to overloading the matrix. They named their technique "surface-enhanced affinity capture mass spectrometry (SEAC)". They further demonstrated their technique by using single stranded DNA which they immobilized on the mass spectrometer probe tip to quasi-isolate the protein lactoferrin from preterm infant urine.—

The paragraph starting on page 5, line 17, has been replaced with the following paragraph:

--The present invention combines and exploits the specificity of antibody-antigen binding and the ability of the mass spectrometer to unequivocally identify molecules in various qualitative and quantitative strategies to analyze one or more antigens or antibodies in a specimen within the limit of detection. Both qualitative and [quantification] quantitative strategies utilize an antibody or antigen to capture and isolate another antigen or antibody, respectively, from its surroundings and thereafter mass spectrometrically analyze the isolated antibody or antigen after release from the capturing agent. This specificity of the antibody-antigen reaction coupled with the ability of the mass spectrometer to separate and unequivocally identify the captured and isolated antibody or antigen by its mass-

to-charge ration from other molecules that may accompany it lends two dimensions of specificity to the present invention.--

The paragraph starting on page 6, line 18, has been replaced with the following paragraph:

--An article by Nelson, R., et al., published in Analytical Chemistry, vol. 67, pp 1153-1158, on or about March 31, 1995, describes certain portions of the present invention in detail [and is herein incorporated by reference].—

The paragraph starting on page 17, line 9, has been replaced with the following paragraph:

--**"Solid substrate"** is defined as any physically separable solid to which an antibody or antigen can be directly or indirectly attached including but not limited to agarose beads, nylon, metals, glass, silicon, and organic membranes.—

The paragraph starting on page 36, line 15, has been replaced with the following paragraph:

--The analyte/IRS signal ratios in the addition-present mass spectral signals are then used to determine the analyte concentration in the addition-absent sample exactly as in the parallel standard addition approach. Since mass spectrometric immunoassay of each addition-present sample serves to calibrate a sample in which the concentration of the analyte differs from the analyte concentration in the addition-free sample by an amount which depends on the amounts of analyte captured in the preceding mass spectrometric immunoassays, it is apparent that the accuracy of this procedure will only be acceptable if the amount of analyte captured in each successive step is small, for example if 5% of the analyte is captured in the mass spectrometric immunoassay of the addition-free sample and mass spectrometric immunoassay of a single addition-present sample is performed, the analyte concentration determined thereby would be in error by 5%.—

The paragraph starting at page 46, line 24, has been replaced with the following paragraph:

--An analytical sample, known to contain 12.5 nM AlAG was mass spectrometrically immunoassayed under similar conditions for the preparations above. The resulting AlAG signal was within that represented on the 5-point working curve of **FIG. 9** and is shown at point **–O-** corresponding to an AlAG concentration of ~12.5 nM which verifies the accuracy of the working curve quantification method.—

In the Claims:

The claims have been amended as follows:

--[48]31. (AMENDED) A method for determining whether a specimen contains [a certain] an analyte species, comprising the steps of:

a. capturing and isolating the [certain] analyte species from the specimen[, said step of capturing and isolating involving the use of] using an affinity reagent having a specific affinity for the [certain] analyte species wherein the affinity reagent includes an antibody immobilized onto a solid substrate;

b. detecting the presence of the isolated [certain] analyte species [through the use of] using a mass spectrometer to determine whether the [certain] analyte species was present in the specimen; and

c. determining the identity of the [certain] analyte species [via] by using molecular weight analysis.—

--[49]32. (AMENDED) The method of claim [48] 31[, further

including] wherein the step of capturing and isolating the sample species includes the steps of:

[a. immobilizing an antibody onto a solid substrate to produce said affinity reagent;]

[b]a. combining an effective amount of the affinity reagent with the specimen until the affinity reagent binds with any of the [certain] analyte species that is present in the specimen to produce a post-combination affinity reagent and an unbound remainder of the specimen;

[c]b. separating the post-combination affinity reagent from the unbound remainder to form an isolated post-combination affinity reagent; and

[d]c. adding a laser desorption/ionization agent to the isolated post-combination affinity reagent to form a mass spectrometric mixture[; and

e. mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained the certain analyte species by exhibiting a mass spectrometric response located at the unique mass-to-charge ratio of the certain analyte species].—

--[50]33. (AMENDED) The method of claim [49] 32 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

--[51]34. (AMENDED) The method of claim [49] 32 further including the step of adding a disassociation agent to the isolated post-combination affinity reagent prior to the step of adding the laser

desorption/ionization agent.—

--[52]35. (AMENDED) The method of claim [51] 34 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

--[53]36. (AMENDED) A method for determining whether a specimen contains [any of] one or more [certain] analyte species, comprising the steps of:

a. capturing and isolating each of the one or more [certain] analyte species from the specimen[, said step of capturing and isolating involving the use of] using an affinity reagent having a specific affinity for each of the one or more [certain] analyte species wherein the affinity reagent includes at least one antibody immobilized onto a solid substrate;

b. detecting the presence of the isolated one or more [certain] analyte species [through the use of] by using a mass spectrometer to determine whether each of the one or more [certain] analyte species was present in the specimen; and

c. determining the identity of the one or more [certain] analyte species [via] by using molecular weight analysis.—

--[54]37. (AMENDED) The method of claim [53] 36[, further including] wherein the step of capturing and isolating each of the one or more analyte species includes the steps of:

[a. immobilizing an antibody onto a solid substrate to produce said affinity reagent;]

[b]a. combining an effective amount of the affinity reagent with the specimen until the affinity reagent binds with each of the one

or more [certain] analyte species that is present in the specimen to produce a post-combination affinity reagent and an unbound remainder of the specimen;

[c]b. separating the post-combination affinity reagent from the unbound remainder to form an isolated post-combination affinity reagent; and

[d]c. adding a laser desorption/ionization agent to the isolated post-combination affinity reagent to form a mass spectrometric mixture[; and

e. mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more certain analyte species by exhibiting a mass spectrometric response located at the unique mass-to-charge ratio of each of the certain analyte species].—

--[55]38. (AMENDED) The method of claim [54] 37 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

--[56]39. (AMENDED) The method of claim [54] 37 further including the step of adding a disassociation agent to the isolated post-combination affinity reagent prior to the step of adding the laser desorption/ionization agent.—

--[57]40. (AMENDED) The method of claim [56] 39 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

--[58]41. (AMENDED) The method of claim [53] 36[, further including] wherein the step of capturing and isolating each of the one or more analyte species includes the steps of:

a. immobilizing a plurality of different antibodies onto a solid substrate to produce said affinity reagent;

b. combining an effective amount of the affinity reagent with the specimen until the affinity reagent binds with each of the one or more [certain] analyte species that is present in the specimen to produce a post-combination affinity reagent and an unbound remainder of the specimen;

c. separating the post-combination affinity reagent from the unbound remainder to form an isolated post-combination affinity reagent; and

d. adding a laser desorption/ionization agent to the isolated post-combination affinity reagent to form a mass spectrometric mixture; and

e. mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more certain analyte species by exhibiting a mass spectrometric response located at the unique mass-to-charge ratio of each of the certain analyte species].—

--[59]42. (AMENDED) The method of claim [58] 41 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

--[60]43. (AMENDED) The method of claim [58] 41 further

including the step of adding a disassociation agent to the isolated post-combination affinity reagent prior to the step of adding the laser desorption/ionization agent.—

--[61]44. (AMENDED) The method of claim [60] 43 wherein the step of combining an effective amount of the affinity reagent with the specimen is accomplished by using a micropipette tip in which there is a filter element [to] which retains the affinity reagent [is bound].—

The following new claims were added:

--45. (NEW) The method of claim 32 wherein the step of detecting the isolated analyte species includes mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained the analyte species by exhibiting a mass spectrometric response located at a unique mass-to-charge ratio of the one or more analyte species.—

--46. (NEW) The method of claim 37 wherein the step of detecting the isolated one or more analyte species includes mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more analyte species by exhibiting a mass spectrometric response located at a unique mass-to-charge ratio of the one or more analyte species.—

--47. (NEW) The method of claim 41 wherein the step of detecting the isolated one or more analyte species includes mass spectrometrically analyzing the mass spectrometric mixture to produce a mass spectrum, said mass spectrum indicating whether the specimen contained each of the one or more analyte species by exhibiting a mass spectrometric response located at a unique mass-to-charge ratio of the analyte species.—